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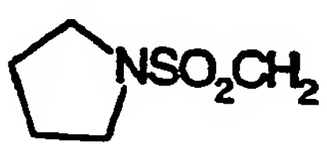
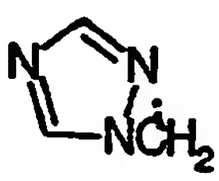
(54) Title: PROCESSES FOR THE PREPARATION OF SUMATRIPTAN AND RELATED COMPOUNDS



(A)



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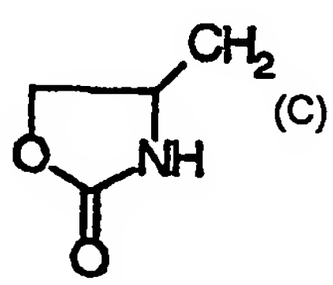

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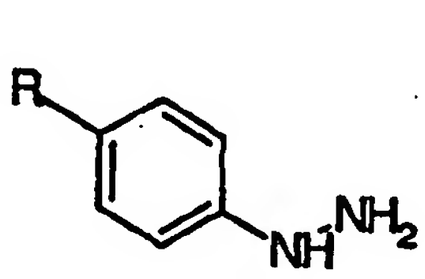
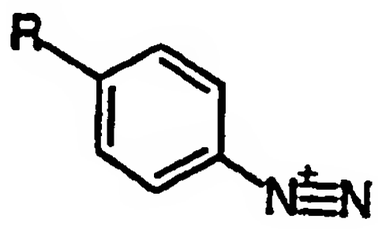


(I)



(II)

(57) Abstract: The present invention relates to a process for preparing phenylhydrazines of formula (I) in which R represents $CH_2SO_2NHCH_3$, $CH_2CH_2SO_2Ph$, $CH_2CH_2SO_2NHMe$ or a group of structure (A), (B), (C), in which a diazonium salt of formula (II) in which X represents an anion derived from hydrochloric acid, sulphuric acid, acetic acid, phosphoric acid, tetrafluoroboric acid or hydrobromic acid is reduced by a dithionite salt. The resulting phenylhydrazines can be converted to the corresponding indole derivatives by the Fischer indole synthesis.

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The present invention relates to processes for preparing phenylhydrazines which are useful intermediates in the preparation of indoles which are useful as therapeutic agents.

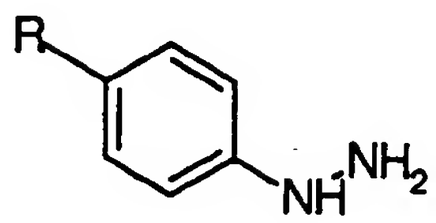
Several indole derivatives are currently on the market or under development as pharmaceuticals. For example, sumatriptan (Glaxo Wellcome) 3–[2–(dimethylamino)ethyl]–*N*–methyl–1*H*–indole–5–methanesulphonamide is currently used in the treatment of migraine. This compound is described in US 4,816,470 and US 5,737,845.

Other indoles of pharmaceutical interest are: almotriptan (WHO Drug Information, Vol.10, No. 4, [1996]), avitriptan (WHO Drug Information, Vol.10, No. 4, [1996]), eletriptan (WHO Drug Information, Vol.9, No. 4, [1995]), frovatriptan (Br.J. Pharmacol. [119, Proc. Suppl., 109P, 1996]), naratriptan, rizatriptan (WHO Drug Information, Vol.10, No. 2, [1996]) and zolmitriptan (J. Med. Chem. [38, No.18, 3566–80, 1995]).

In the preparation of such indoles phenylhydrazines are key intermediates which may be cyclised into indoles using the well known Fischer indole synthesis. In US 4,816,470 the method of preparation of such compounds involves the diazotisation of an aniline followed by reduction of the diazonium salt obtained with stannous chloride dihydrate. We have found that the use of tin reagents in this reduction presents a number of problems. Firstly there are environmental issues relating to the disposal of toxic wastes containing tin residues. Secondly, low temperature vessels are required to carry out the reduction and thirdly it is often difficult to remove the last traces of tin salts from the intermediate and from later stages of the reaction sequence.

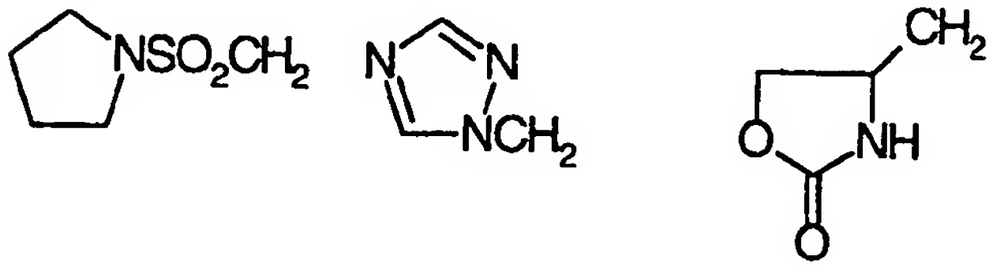
Surprisingly a process has been found which uses a cheaper reducing agent which causes minimal environmental problems. In addition the process does not require the use of low temperature vessels, allows the telescoping of the process, i.e. that is the combination of more than one step, and increases the purity of the intermediate obtained and further products in the reaction sequence.

The present invention provides a process for preparing a compound of formula I including salts thereof

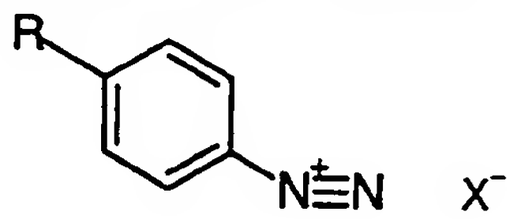


I

wherein R represents $CH_2SO_2NHCH_3$, $CH_2CH_2SO_2Ph$, $CH_2CH_2SO_2NHMe$ or a group of structure:



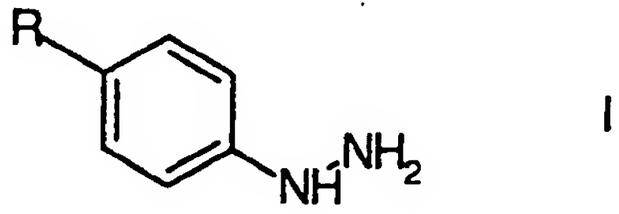
comprising the reduction of a diazonium salt of formula II



II

in which R is as previously defined and X^- represents an anion derived from hydrochloric acid, sulphuric acid, acetic acid, phosphoric acid, tetrafluoroboric acid or hydrobromic acid, with a dithionite salt.

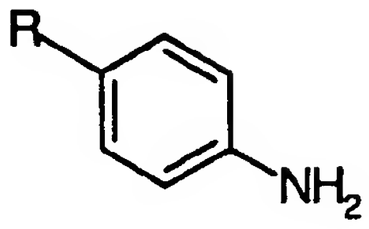
In another aspect the present invention provides a process for preparing a compound of formula I or a salt thereof



I

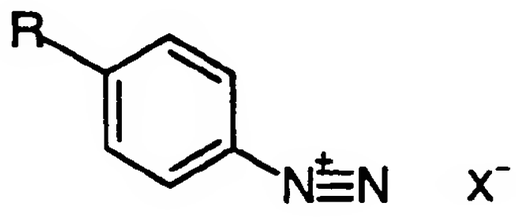
in which R is as previously defined comprising the steps of

a) reacting a compound of formula III or salt thereof



III

in which R is as previously defined with a diazotising agent optionally in the presence of acid to give a diazonium salt of formula II



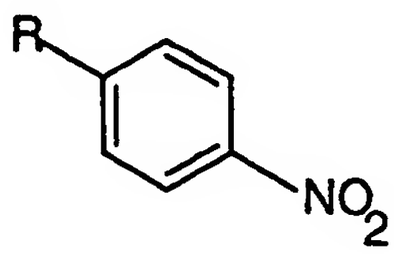
II

in which R and X^- are as previously defined and

b) reducing the diazonium salt with a dithionite salt to give the compound of formula I.

Suitable salts of the compounds of formula I and III include acid addition salts formed with organic or inorganic acids for example hydrochlorides, hydrobromides, sulphates, nitrates, phosphates, formates, mesylates, citrates, benzoates, fumarates, maleates, toluene–p–sulphonates and succinates. Preferably the salt is the hydrochloride or hydrobromide salt .

In a further aspect the present invention provides a process in which the compound of formula III or salt thereof as previously defined is prepared by reacting a compound of formula IV

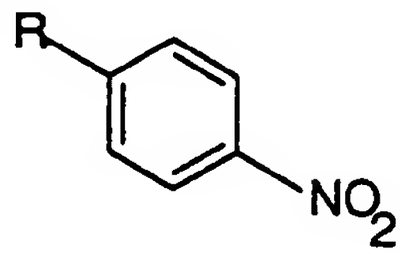


IV

in which R is as previously defined with a reducing agent, optionally in the presence of an acid or with an additional salt formation step eg reaction with an acid, where a salt of the compound of formula III is required. Preferably the compound of formula III is used without isolation.

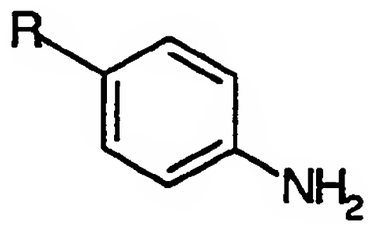
Consequently the present invention provides a process for the preparation of a compound of formula I which comprises the steps of:

a) reacting a compound of formula IV



IV

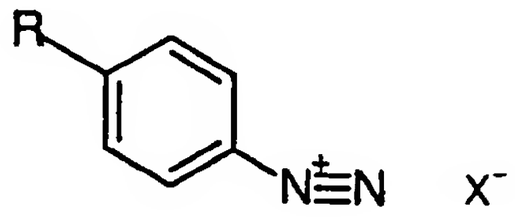
in which R is as previously defined with a reducing agent to give a compound of formula III



III

in which R is as previously defined and

b) reacting the compound of formula III with a diazotising agent optionally in the presence of acid to give a diazonium salt of formula II

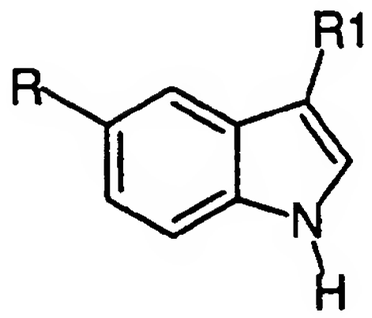


II

in which R and X^- are as previously defined and

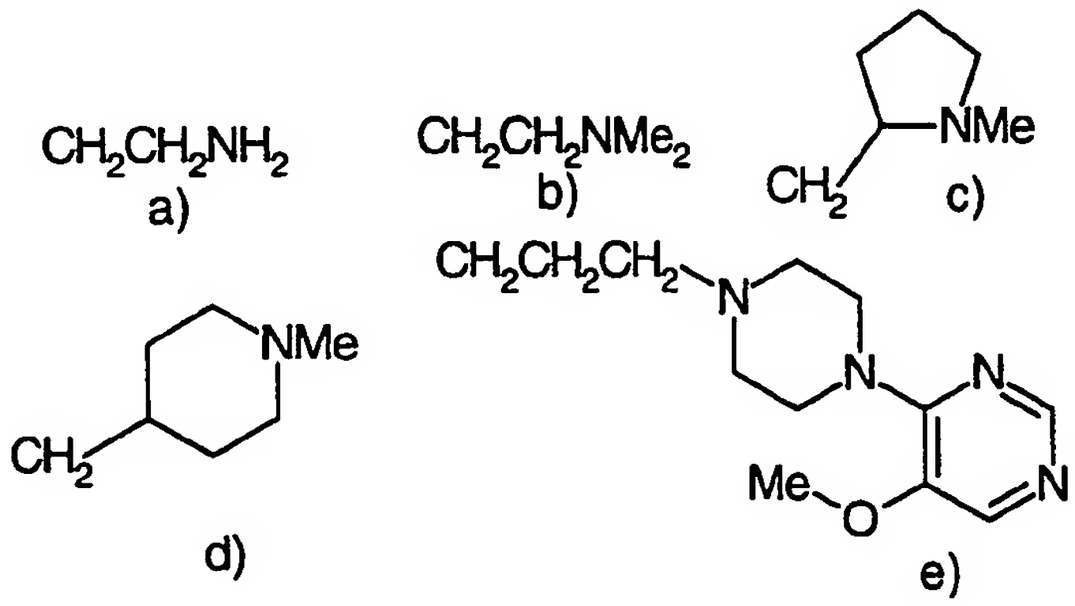
c) reducing the diazonium salt with a dithionite salt to give the compound of formula I.

In a further aspect the present invention comprises a process for preparing a compound of formula V



V

including pharmaceutically acceptable salts thereof in which R is as previously defined and R1 is a group of formula a), b), c), d), or e)



comprising performing a Fischer Indole synthesis by reacting a compound of formula I with an aldehyde of formula VI in which R1 is as previously defined optionally in the presence of an acid catalyst.

$R1CH_2CHO$

VI

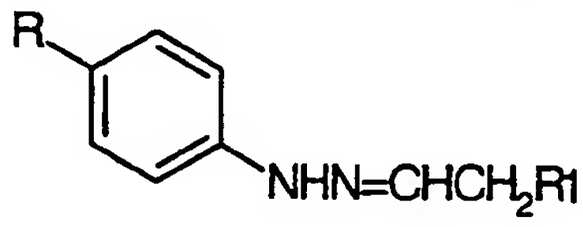
Optionally a protected form of the aldehyde such as an acetal may be used this reaction. Optionally an aldehyde or a protected form of the aldehyde of formula VII may be used where R2 is a group capable of being transformed into a group R1 upon cyclisation to a compound of formula V, for instance when R2 is $-CH_2CH_2Cl$ to give compounds of formula V with R1 is $-CH2CH2NH_2$ using the well known Grandberg version of the Fischer Indole synthesis.

$R2CH_2CHO$

VII

Optionally it may be preferred to synthesise one compound of formula V by reacting another compound of formula V, for instance, when R1 is $CH_2CH_2NMe_2$ by reductive alkylation of the compound V where R1 is $CH_2CH_2NH_2$

Optionally it may be preferred to isolate the intermediate hydrazone VIII



VIII

In which R and R1 are as previously defined prior to performing the cyclisation to V.

Suitably the diazotising agent is a metal nitrite salt or alkyl nitrite. Preferably the diazotising agent is sodium nitrite or butyl nitrite. Most preferably the diazotising agent is sodium nitrite.

Suitably the diazotising agent is present in the range of 0.5–3 molar equivalents with respect to the compound of formula II. Preferably the diazotising agent is present in the range of 0.8–1.5 molar equivalents with respect to the compound of formula II. More preferably the diazotising agent is present in the range of 0.9–1.1 molar equivalents with respect to the compound of formula II.

Optionally it may be preferred to add a reagent, for example sulphamic acid, to destroy excess nitrous acid at the end of this step.

Suitably the acid is hydrochloric acid, sulphuric acid, acetic acid, phosphoric acid, tetrafluoroboric acid or hydrobromic acid. Preferably the acid is hydrochloric acid.

Suitably the acid is present in the range of 1–10 molar equivalents with respect to the compound of formula II. Preferably the acid is present in the range of 2–8 molar equivalents with respect to the compound of formula II. More preferably the acid is present in the range of 3–6 molar equivalents with respect to the compound of formula II.

Suitably the dithionite salt is a metal dithionite salt. Most preferably the dithionite salt is sodium dithionite.

Suitably the dithionite is present in the range of 1–5 molar equivalents with respect to the compound of formula II and is used as an aqueous solution or suspension in the presence of base, preferably sodium hydroxide. Preferably the dithionite is present in the range of 2–4 molar equivalents with respect to the compound of formula II and is used as an aqueous solution or suspension in the presence of base, preferably sodium hydroxide. Preferably isopropanol can be used as a co-solvent to reduce foaming.

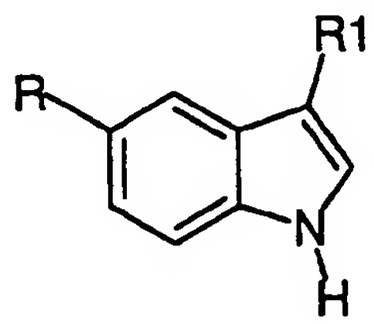
Suitably the diazotisation step is carried out at a temperature in the range of –20°C to +20°C. Preferably the diazotisation step is carried out at a temperature in the range of –10°C to +10°C. More preferably the diazotisation step is carried out at a temperature in the range of –5°C to +5°C.

Suitably the reduction of the diazonium salt is carried out at a temperature in the range of –50°C to +50°C. Preferably the reduction of the diazonium salt is carried out at a temperature in the range of –10°C to +30°C. More preferably the reduction of the diazonium salt is carried out at a temperature in the range of –5°C to +25°C.

Suitably the reducing agent for the nitro compound is hydrogen in the presence of a catalyst, sodium dithionite, iron in the presence of acid or lithium aluminium hydride. Preferably the reducing agent for the nitro compound is hydrogen in the presence of a catalyst, sodium dithionite, or lithium aluminium hydride. Most preferably the reducing agent for the nitro compound is hydrogen in the presence of a palladium catalyst.

The hydrogenation/diazonium reaction/reduction can be carried out as a one-pot reaction.

In a further aspect the present invention provides a process in which a compound of formula V



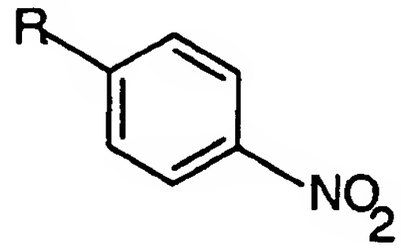
V

in which R is $CH_2SO_2NHCH_3$ and R1 is $CH_2CH_2NMe_2$, is prepared by reacting a compound

of formula V, in which R is $CH_2SO_2NHCH_3$ and R1 is $CH_2CH_2NH_2$, with a reducing agent and a formaldehyde equivalent in the presence of a buffer.

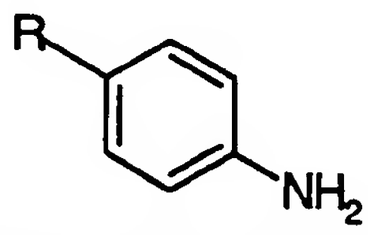
In another aspect the present invention provides a process for the preparation of sumatriptan or a pharmaceutically acceptable salt thereof comprising the following steps:

a) reducing a compound of formula



IV

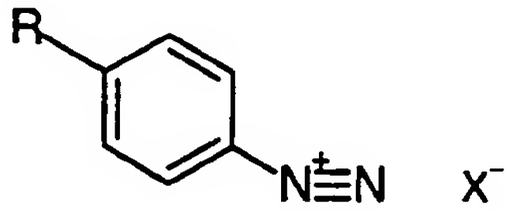
in which R is $CH_2SO_2NHCH_3$ with a reducing agent, optionally in the presence of an acid to give a compound of formula III



III

or optionally a salt thereof in which R is $CH_2SO_2NHCH_3$ and

b) reacting the compound of formula III with a diazotising agent optionally in the presence of acid to give a compound of formula II

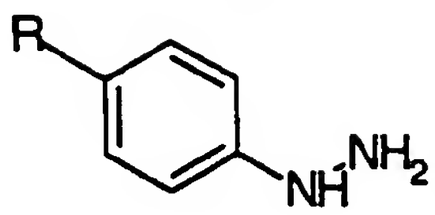


II

in which R is $CH_2SO_2NHCH_3$ and X^- represents a chloride, bromide, acetate, hydrosulphate or phosphate anion and

c) reducing the compound of formula II with a dithionite salt to give a compound of formula I

in which R is $CH_2SO_2NHCH_3$ and



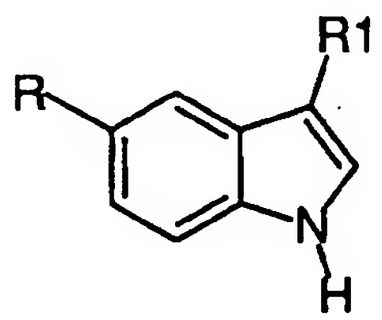
I

d) reacting the compound of formula I in which R is $CH_2SO_2NHCH_3$ with an aldehyde of formula VII

$R2CH_2CHO$

VII

in which R2 represents $ClCH_2CH_2$– and the aldehyde group is protected as an acetal (preferably the dimethyl acetal) in the presence of a buffer optionally in the presence of an acid catalyst to give a compound of formula V



V

or a salt thereof in which R is $CH_2SO_2NHCH_3$ and R1 is $CH_2CH_2NH_2$ and

e) reacting the compound of formula V obtained in d) with a formaldehyde equivalent and a reducing agent in the presence of a buffer to give a compound of formula V in which R is $CH_2SO_2NHCH_3$ and R1 is $CH_2CH_2NMe_2$ or a pharmaceutically acceptable salt thereof.

Preferably none of the intermediate compounds is isolated in this process.

Suitably the reducing agent is a hydride equivalent such as sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride and lithium aluminium hydride. Preferably the reducing agent is sodium borohydride or sodium cyanoborohydride. Most preferably the reducing agent is sodium borohydride.

Suitably the reducing agent is present in the range of 0.25 – 5 molar equivalents with respect to the compound of formula V. Preferably the reducing agent is present in the range of 0.5 – 4 molar equivalents with respect to the compound of formula V. More preferably the

reducing agent is present in the range of 0.75 – 3 molar equivalents with respect to the compound of formula V.

Suitably the formaldehyde equivalent is formaldehyde, paraformaldehyde or dimethoxymethane. Preferably the formaldehyde equivalent is formaldehyde or paraformaldehyde. Most preferably the formaldehyde equivalent is formaldehyde as an aqueous solution.

Suitably the formaldehyde equivalent is present in the range of 0.5 – 18 molar equivalents with respect to the compound of formula V. Preferably the formaldehyde equivalent is present in the range of 1 – 10 molar equivalents with respect to the compound of formula V. More preferably the formaldehyde equivalent is present in the range of 1.9 – 5 molar equivalents with respect to the compound of formula V.

Suitably the buffer used keeps the pH of the reaction solution between pH 6 and pH 14. Preferably the buffer keeps the pH of the reaction solution between pH 7 and pH 11. More preferably the buffer keeps the pH of the reaction solution between pH 8 and pH 10. Most preferably the buffer is sodium hydrogenphosphate.

Suitably the buffer is present in the range of 0.1 – 10 molar equivalents with respect to the compound of formula V. Preferably the buffer is present in the range of 0.2 – 5 molar equivalents with respect to the compound of formula V. Most preferably the buffer is present in the range of 0.5 – 3 molar equivalents with respect to the compound of formula V.

Suitable pharmaceutically acceptable salts of the compound of formula V (including sumatriptan) include acid addition salts formed with organic or inorganic acids for example hydrochlorides, hydrobromides, sulphates, nitrates, phosphates, formates, mesylates, citrates, benzoates, fumarates, maleates and succinates. Other salts may be useful in the preparation of the compound of formula I e.g. creatinine sulphate adducts, and salts with e.g. toluene–p–sulphonic acid. When the compound of formula V is sumatriptan the salt is preferably the succinate salt or the hemisulphate salt .

The invention is illustrated by the following Examples which are given by way of example only. The final products of each of these Examples were characterised by one or more of the following procedures: high performance liquid chromatography, elemental analysis, nuclear magnetic resonance spectroscopy, mass spectroscopy and infrared spectroscopy.

EXAMPLES

Example 1

a) A stirred mixture of 4–amino–*N*–methylbenzenemethanesulphonamide (35.6 g), concentrated hydrochloric acid (83.7 ml) and water (314 ml) was heated at 50°C for 15 minutes and the solution then cooled to –5°C. A solution of sodium nitrite (12.5 g) in water (21 ml) was then added dropwise over 10 minutes. The resulting solution was stirred for 1 hour and then added over 10 minutes to a stirred suspension of sodium dithionite (sodium hydrosulphite) (96.1 g) in water (420 ml) and 46/48% w/w sodium hydroxide solution (34 ml) at –5°C to +5°C. The suspension was stirred for 2.75 hours. 46/48% w/w Sodium hydroxide (22 ml) was added and the mixture was stirred for 20 minutes at 20°C and then for 40 minutes at 0–5°C. The mixture was filtered and the product was washed with water (3 x 110 ml) and dried to give the free base of the product.

The free base of the product (31.5 g) and ethanol (315 ml) were stirred and heated to reflux. Concentrated hydrochloric acid (12.3 ml) was added followed by ethanol (155 ml). The mixture was boiled under reflux for 10 minutes and then cooled to 0°C. The product was collected by filtration, washed with ethanol (155 ml) and dried to give 4–hydrazino–*N*–methylbenzenemethanesulphonamide hydrochloride, yield 31.4 g.

b) Absolute ethanol (50 ml) was added to a stirred suspension of 4–hydrazino–*N*–methylbenzenemethanesulphonamide hydrochloride (6.42 g) in water (20ml) and the mixture was stirred for 10 minutes. 4–Chlorobutanal dimethyl acetal (3.85 g) was added and washed in with more absolute ethanol (11.7 ml). 2M Hydrochloric acid (0.22 ml) was added and the solution was stirred at ambient temperature for 4.5 hours. Sodium hydrogenphosphate (3.01 g) was added and the mixture was stirred at ambient temperature for 10 minutes and then gradually heated to boiling under reflux over 40 minutes. The mixture was stirred and boiled under reflux for a further 3 hours and then allowed to stand for 16 hours at ambient temperature. The mixture was concentrated under reduced pressure (around 60 ml removed) and then dichloromethane (25 ml) and water (25 ml) were added, followed by potassium carbonate (0.74 g). At this point the pH was 5. The mixture was filtered and the filtrate was separated. The aqueous layer was washed with more dichloromethane

(2 x 25 ml) and the combined organic layer and washings were evaporated to dryness under reduced pressure to give a solid by–product, yield 1.60 g.

The aqueous layer was mixed with dichloromethane (125 ml), absolute ethanol (60 ml) potassium carbonate (37 g) and water (12 ml). The mixture was stirred for 35 minutes and then separated. The organic layer was treated with charcoal and stirred at ambient temperature for 1 hour. The mixture was filtered and the filtrate was concentrated to a mass of 20 g under reduced pressure. The mixture was stirred for 1 hour and isopropyl acetate (62 ml) was added and the suspension was stirred for 64 hours. The solid was collected by filtration, washed with more isopropyl acetate (10 ml) and dried under vacuum at 50°C to give 3–(2–aminoethyl–*N*–methyl–1*H*–indole–5–methanesulphonamide, yield 3.64 g (53.4%). Purity 93.63%.

Comparative Example

4–Hydrazino–*N*–methylbenzenemethanesulphonamide hydrochloride, which had been prepared by diazotisation of 4–amino–*N*–methylbenzenemethanesulphonamide with sodium nitrite and then reduced with tin chloride, was reacted according to the procedure of Example 2. 3–(2–Aminoethyl–*N*–methyl–1*H*–indole–5–methanesulphonamide was obtained in a yield of 48.8% and was found to be 92.25% pure by HPLC.

Example 2

N–Methyl–4–nitrobenzenemethanesulphonamide (46.0 g, 0.23 mol), 10% palladium on carbon (4.6 g) and 2M hydrochloric acid (180 ml) in water (200 ml) were stirred for 1.5 hours under 2.5 atmospheres of hydrogen at 20°C. The reaction mixture was then filtered through a celite bed and washed with further water (100 ml). A portion of this filtrate (50 ml) was taken and then diluted with concentrated hydrochloric acid (12.7 ml). The stirred suspension was cooled to below 0°C and a solution of sodium nitrite (2.2 g, 32 mmol) in water (4 ml) added dropwise over 20 minutes under an atmosphere of nitrogen. After stirring for 15 minutes, the clear solution was transferred *via* a cannula to a solution of sodium dithionite (17.0 g, 98 mmol) and 46/48% w/w sodium hydroxide (5.9 ml) in water (75 ml) at –5°C. The mixture was then warmed to room temperature and stirred for a further 2.5 hours. 46/48% w/w sodium hydroxide (6.5 ml) was then added until the pH of the solution was approximately 9. Stirring at room temperature was continued for a further 0.5 hours

followed by cooling in an ice bath for 0.5 hours. Filtration of the reaction mixture gave 4–hydrazino–*N*–methylbenzenemethanesulphonamide as an off–white solid (2.5 g, 48%)

Example 3

A stirred mixture of 4-amino-N-methylbenzenemethanesulphonamide (50.0 g, 0.25 mmol), conc. hydrochlorid acid (117 ml) and water (356 ml) was heated at 50°C for 15 minutes and the solution then cooled to -5°C. A solution of sodium nitrite (17.5 g) in water (30 ml) was then added dropwise over 15 minutes and the resulting solution stirred for a further 15 minutes. The reaction mixture was then added via a cannula to a stirred suspension of sodium dithionite (135 g, 0.66 mol), water (365 ml), 46/48% w/w sodium hydroxide solution (23.5 ml) and IPA (40 ml) at -5°C. The temperature was kept around -5°C during the 40 minute addition. The suspension was then warmed to room temperature and stirred for 2.5 hours before 46/48% w/w Sodium hydroxide (53.5 ml) was added to give a pH of 7-8. Finally, the mixture was stirred for 30 minutes, product filtered and then washed with water (123 ml) to give a cream solid.

To form the hydrochloride salt, conc. hydrochloric acid (20 ml) was added to the free base suspended in isopropanol (400 ml) at ambient. After stirring for 15 minutes, the product was collected by filtration, washed with isopropanol (125 ml) and dried to give 4-hydrazino-N-methylbenzenemethanesulphonamide hydrochloride (45.7 g, 73% at 97% purity by HPLC).

Example 4

N-Methyl-4-nitrobenzenemethanesulphonamide (23.0 g, 0.1 mol), 5% palladium on carbon (9.4 g) and conc. hydrochloric acid (11 ml) in water (245 ml) were stirred for 2 hours under 5 atmospheres of hydrogen at 50°C. The reaction mixture was then filtered through a celite bed and washed with further conc. hydrochloric acid (6 ml) in water (34 ml). The filtrate was then diluted with conc. hydrochloric acid (30 ml) and the solution cooled to -5°C to give a suspension. Sodium nitrite (7.0 g, 0.101 mol) in water (12 ml) was then added dropwise over 20 minutes keeping the temperature around -5°C. After stirring for 15 minutes, the clear solution was transferred via a cannula to a solution of sodium dithionite (54.0 g, 0.264 mol), 46/48% w/w sodium hydroxide (9.4 ml), water (197 ml) and isopropanol (20 ml) at -5°C. The temperature was kept around -5°C during the 40 minutes addition. The mixture was then warmed to room temperature and stirred for a further 2.5 hours. 46/48% w/w sodium hydroxide (21.4 ml) was then added until the pH of the solution was approximately

7.8. Stirring at room temperature was continued for a further 0.5 hours followed by filtration of the reaction mixture, washing with water (50 ml) and then isopropanol (150 ml) to give 4-hydrazino-N-methylbenzenemethanesulphonamide as an of-white solid. Forming the hydrochloride salt as above, gave an overall yield of 77% at 97.6% purity by HPLC.

Example 5

3-(2-Aminoethyl)-*N*-methyl-1*H*-indole-5-methanesulphonamide (5.0 g, 18.7 mmol), prepared by the method of Example 1, and sodium hydrogenphosphate (5.0 g, 35.2 mmol) were heated to 40°C in methanol (50 ml) for 15 minutes and then recooled to room temperature. Solutions of 37% aqueous formaldehyde (5 ml) and sodium borohydride (0.72 g) in water (5 ml stabilised with one drop of 46/48% w/w sodium hydroxide) were added simultaneously over one hour at a temperature between 17 and 21°C. The mixture was stirred at room temperature for a further 0.5 hours, then filtered and the filter bed washed with methanol (10 ml). The combined filtrates were then adjusted to pH 6 by addition of 4M hydrochloric acid, concentrated under reduced pressure (to approximately 20 g) and acidified to pH 1 with more 4M hydrochloric acid. Ethyl acetate (30 ml) was added and then potassium carbonate was added to give a pH about 11 and the product extracted in a separating funnel. The aqueous layer was further extracted with ethyl acetate (30 ml) and the combined organic layers dried over sodium sulphate, filtered and concentrated to give sumatriptan free base (4.7 g, 85%, HPLC showed 87% compound).

This material was of suitable quality for conversion into sumatriptan mono–succinate or sumatriptan hemisulphate as described in GB 2,162,522 and EP 490,689 respectively.

Example 6

3-(2-Aminoethyl)-N-methyl-1H-indole-5-methanesulphonamide hydrochloride (50.0 g, 0.165 mol) and sodium hydrogenphosphate (47.0 g) was heated to 45°C in methanol (420 ml). To this mixture sodium methoxide (29 ml) was added and the solution was cooled to room temperature. Separate solutions of 37% aqueous formaldehyde (53 ml) in methanol (7 ml) and sodium borohydride (10.0 g) in water (49 ml stabilised with two drops of 46/48% w/w sodium hydroxide) were then added simultaneously over one hour at a temperature between 17-21°C. Stirring the mixture at room temperature for a further 1 hour was followed by adjustment of the solution to pH 6 by addition of conc. HCl (42 ml) in water (83 ml). The suspension was then removed by filtration and the filter bed washed with methanol (59 ml). Further water (90 ml) was added to the filtrate and then the mixture was

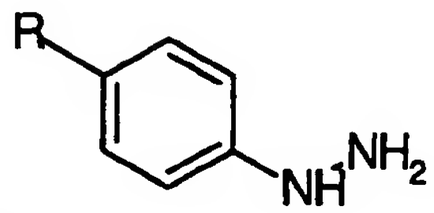
concentrated to remove the residual methanol. Adjustment of the aqueous solution to pH 2 using conc. HCl, addition of ethyl acetate (100 ml) and methanol (10 ml), was followed by basification with potassium carbonate (90 g) in water (130 ml). This precipitated a grey solid that was collected by filtration, washed with water (2 X 100 ml) and then washed with ethyl acetate (100 ml) to give sumatriptan free base (42.4 g, 87%, HPLC showed 98% compound).

Comparative Example.

3-(2-Aminoethyl)-*N*-methyl-1*H*-indole-5-methanesulphonamide was reacted in a similar fashion to example 3 without the inclusion of the sodium hydrogenphosphate buffer. The product free base was obtained in 40% yield and in a purity of 60% by HPLC.

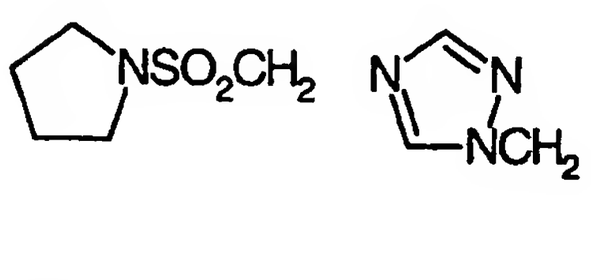
Claims

1) A process for preparing a compound of formula I including salts thereof

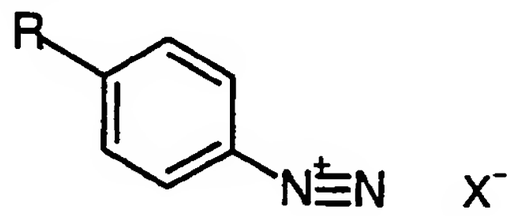


I

wherein R represents $CH_2SO_2NHCH_3$, $CH_2CH_2SO_2Ph$, $CH_2CH_2SO_2NHMe$ or a group of structure:



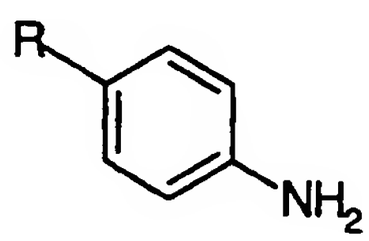
comprising the reduction of a diazonium salt of formula II



II

in which R is as previously defined and X^- represents an anion derived from hydrochloric acid, sulphuric acid, acetic acid, phosphoric acid, tetrafluoroboric acid or hydrobromic acid with a dithionite salt.

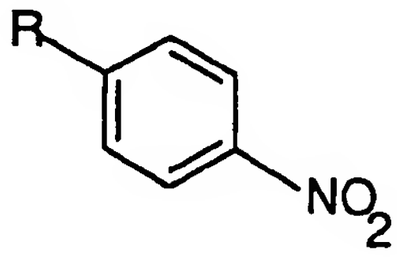
2) A process according to claim 1 wherein the compound of formula II is prepared by reacting a compound of formula III or salt thereof



III

in which R and X- represents a chloride, bromide, acetate, hydrosulphate or phosphate anion as previously defined with a diazotising agent optionally in the presence of acid.

3) A process according to either claim 1 or claim 2 wherein the compound of formula III is prepared by reacting a compound of formula IV



IV

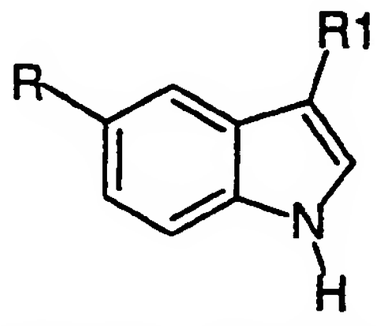
in which R is as previously defined with a reducing agent, optionally in the presence of an acid.

4) A process according to claim 1 wherein the compound of formula I is further reacted with an aldehyde of formula VI in which R1 is as previously defined optionally in the presence of an acid catalyst

$R1CH_2CH_2CHO$

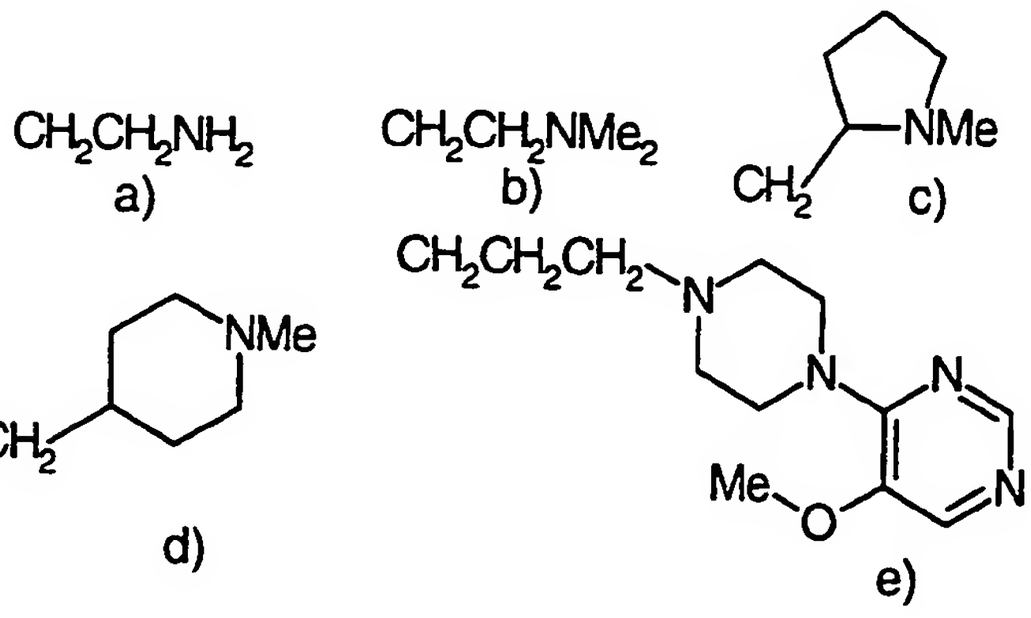
VI

to give a compound of formula V



V

in which R is as previously defined and R1 is a group of formula a), b), c), d), or e):



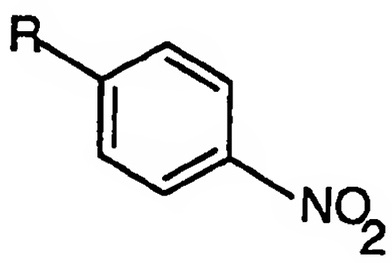
comprising performing a Fischer Indole synthesis by reacting a compound of formula I with an aldehyde of formula VI in which R1 is as previously defined optionally in the presence of an acid catalyst.

5) A process according to claim 4 in which in the compound of formula I R is $CH_2SO_2NHCH_3$ and in the compound of formula VI R1 is $CH_2CH_2NH_2$ and in the compound of formula V obtained has R is $CH_2SO_2NHCH_3$ and R1 is $CH_2CH_2NH_2$.

6) A process according to claim 5 wherein the compound of formula V in which R is $CH_2SO_2NHCH_3$ and R1 is $CH_2CH_2NH_2$ is reacted with a formaldehyde equivalent and a reducing agent in the presence of a buffer to give a compound of formula V in which R is $CH_2SO_2NHCH_3$ and R1 is $CH_2CH_2NMe_2$.

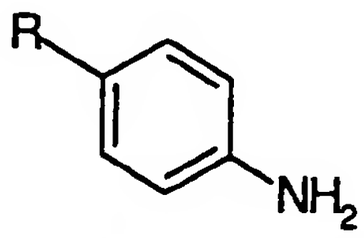
7) A process for the preparation of sumatriptan or a pharmaceutically acceptable salt thereof comprising the following steps:

a) reducing a compound of formula



IV

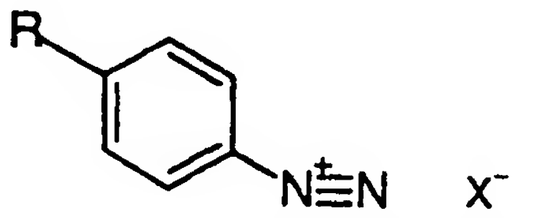
in which R is $CH_2SO_2NHCH_3$ with a reducing agent, optionally in the presence of an acid to give a compound of formula III



III

or optionally a salt thereof in which R is $CH_2SO_2NHCH_3$ and

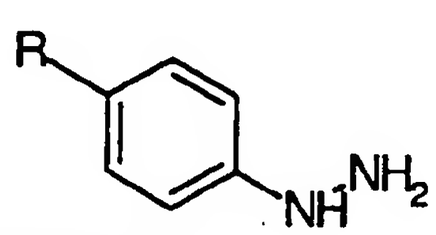
b) reacting the compound of formula III with a diazotising agent optionally in the presence of acid to give a compound of formula II



II

in which R is $CH_2SO_2NHCH_3$ and X^- represents a chloride, bromide, acetate, hydrosulphate or phosphate anion and

c) reducing the compound of formula II with a dithionite salt to give a compound of formula I



I

in which R is $CH_2SO_2NHCH_3$ and

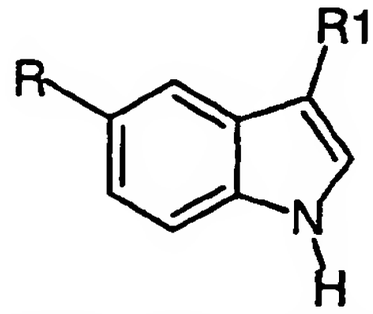
d) reacting the compound of formula I in which R is $CH_2SO_2NHCH_3$ with an aldehyde of formula VII

R2CH_2CHO

VII

in which R2 represents $ClCH_2CH_2$– and the aldehyde group is protected as an acetal in the presence of a buffer optionally in the presence of an acid catalyst to give a compound of formula V

R1



V

or a salt thereof in which R is $CH_2SO_2NHCH_3$ and R1 is $CH_2CH_2NH_2$ and

e) reacting the compound of formula V obtained in d) with a formaldehyde equivalent and a reducing agent in the presence of a buffer to give a compound of formula V in which R is $CH_2SO_2NHCH_3$ and R1 is $CH_2CH_2NMe_2$ or a pharmaceutically acceptable salt thereof.

8) A process according to claim 7 in which none of the intermediate compounds is isolated.

9) A process according to claim 7 wherein the salt is the succinate salt.

10) A process according to claim 7 wherein the salt is the hemisulphate salt.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 00/10581

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C303/40 C07C311/35 C07D209/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 February 2001	23/02/2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl. Fax (+31-70) 340-3016	Authorized officer English, R

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INTERNATIONAL SEARCH REPORT

Int :ional Application No
PCT/EP 00/10581

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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